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ABSTRACT

This fact sheet summarizes the interrelations of Down syndrome and Alzheimer disease in a question and answer format. The following questions are addressed: What is Alzheimer disease? Why is a relationship suggested between Down syndrome and Alzheimer disease? Is there a genetic link between Alzheimer disease and Down syndrome? Why is a relationship between Alzheimer disease and Down syndrome doubted? Is dementia defined differently in persons with Alzheimer disease than in persons with Down syndrome? How can the research on the effects of Alzheimer disease in people with Down syndrome be summarized? What is the relation of aging to dementia in people with Down syndrome? What does the future hold for treatment and prevention? A source for further information is also given. (DB)

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INTERRELATIONS OF DOWN SYNDROME AND ALZHEIMER DISEASE

by Miriam Schweber, Ph.D.

What is Alzheimer disease?

Alzheimer disease is a devastating condition that is expressed on three levels. **Anatomically,** localized areas of the brain become infested with abnormal structures and undergo extensive losses of neurons. **Biochemically,** specific changes are found in certain brain regions. **Behaviorally,** progressive memory loss and changes in personality occur (referred to as dementia). It is estimated that Alzheimer disease affects more than 3 million United States' citizens. It is the fourth most common cause of death for those over age 65, and accounts for one third of all those in nursing homes.

Why is a relationship suggested between Down syndrome and Alzheimer disease?

A relationship between Alzheimer disease and Down syndrome was proposed originally because of **anatomical** findings. Adults with Down syndrome were found to have the abnormal brain changes characteristic of Alzheimer disease. A worldwide survey of autopsy results has been done with analysis of more than 200 accounts of individuals with Down syndrome over age 35, 500 under age 35, and 1,000 non-Down syndrome individuals with mental retardation. Autopsy results indicate that all people with Down syndrome over the age of 36 display the typical brain abnormalities associated with Alzheimer disease.

Starting in the late 1970s, **biochemical** alterations have been discovered in the brains of victims of Alzheimer disease. Almost all of these changes have now also been found for older, but not younger, persons with Down syndrome in identical systems and locations. In general, the severity of changes found has been greater in adults with Down syndrome than in people with Alzheimer disease. In addition, virtually identical abnormal proteins have now been found in the brains of older people with Down syndrome and those with Alzheimer disease.

Thus, laboratory findings indicate that two of the three levels of manifestation of Alzheimer disease occur identically in people with Alzheimer disease and in older adults with Down syndrome.

Is there a genetic link between Alzheimer disease and Down syndrome?

The possibility of a genetic association comes from studies that have found an increased incidence of Down syndrome in the families of individuals with Alzheimer disease. This increase is not statistically significant among first degree relatives (parents and children), but is found when second and third degree relatives are included.

The question of genetic involvement in Alzheimer disease is currently being intensively investigated, especially with reference to Down syndrome. One area of exploration involves the use of a mouse model for Down syndrome. Many of the Alzheimer disease biochemical abnormalities have already been found in such mice. These results, plus the presence of the virtually identical abnormal proteins found in the brains of victims of Alzheimer disease and adults with Down syndrome, imply that a genetic correlation between Alzheimer disease and Down syndrome may be important.

Why is a relationship between Alzheimer disease and Down syndrome doubted?

While the identity of alterations on the anatomical and biochemical levels has suggested a relationship between Alzheimer disease and Down syndrome, doubts of an association have been raised because of findings on the **behavioral** level. Various individual studies have reported that 20-35 percent of adults with Down syndrome studied exhibited gross behavioral changes. Almost all of these persons also had seizures. Another 25 percent were recorded as having seizures without behavioral changes. The remaining 50 percent had no indications of severe behavioral changes. Yet all of the individuals studied were recorded as having the anatomical brain abnormalities of Alzheimer disease. Based on the limited studies done so far, it appears likely that they had the biochemical changes as well.

This disparity between all adults with Down syndrome having anatomical brain abnormalities and the 25 percent exhibiting behavioral changes has been difficult to understand. Some scientists simply state that all adults with Down syndrome develop Alzheimer disease because of the universality of the laboratory findings; others argue that most adults with Down syndrome do not have Alzheimer disease because they are unaffected behaviorally. Some investigators have been aware of the difficulty of defining dementia in people with mental retardation and have searched for subtle signs of mental deterioration with age. Some minor deficits have been found in older people with Down syndrome, including losses in short term memory and in visual retention. Whether these changes are due to normal aging or are evidence of behavioral symptoms of Alzheimer disease in Down syndrome is a subject of debate.

Is dementia defined differently in persons with Alzheimer disease than in persons with Down syndrome?

The type of dementia that is described for Alzheimer disease is unusual, involving maintenance of personality structure until very late in the disease with losses in cognitive abilities predominating in the early stages. The diagnosis of dementia in Alzheimer disease is reached because of problems encountered in meeting the demands of our highly complex society. Yet such persons can often continue to function on a social level in a supported environment for many years. In one compilation of stages of Alzheimer disease, individuals two-thirds of the way through the course

of the disease were said to retain knowledge of major facts and require no assistance with toileting, eating or dressing (except that they may put their shoes on the wrong feet). However, they may not know their address or phone number, may be disoriented with respect to time and place, and are unable to count backward from 40 by 4s.

In people with Down syndrome, a diagnosis of dementia is noted in institutional records when individuals develop incontinence, exhibit marked personality changes and become hostile, apathetic and then withdrawn. A dramatic loss of brain weight occurs among adults with Down syndrome who are so diagnosed, indicating that marked physical alterations accompany the behavioral changes. These effects are associated only with the last stages of Alzheimer disease for the population which is not retarded. Thus, it is possible that the early stages of Alzheimer disease may involve some losses in abilities and levels of function that many people with Down syndrome never acquire.

How can the research on the effects of Alzheimer disease in people with Down syndrome be summarized?

From the laboratory perspective, all older people with Down syndrome will develop Alzheimer disease since they will all acquire the anatomical and biochemical changes of the disease. But at the third, behavioral level, Alzheimer disease may not be expressed in the majority of adults with Down syndrome except in quiet subtle ways. One half or so of older people with Down syndrome will live out their lives without exhibiting any major behavioral changes; one fourth will develop seizures but not gross changes in behavior, and one fourth will develop the behavioral changes defined as dementia in Down syndrome. The point to be stressed is that current research indicates that three fourths of all individuals with Down syndrome will live out their lives with only minor modifications of personality or mental ability, with life spans ranging into the 70s.

What is the relation of aging to dementia in people with Down syndrome?

Although the life expectancy of people with Down syndrome is still considerably less than the general population, it has been increasing markedly in recent years. Currently, about one out of four persons with Down syndrome can be expected to live past age 50 with significant numbers living into their 70s. The question of the possible effects of Alzheimer disease in this population thus becomes significant for public health policy considerations as well as family concerns.

One unexpected finding of the autopsy survey results was that the percentage of persons with Down syndrome who exhibited gross personality change did not increase with age. (The percentage diagnosed with dementia was statistically the same for each ten year age interval over age 40.) Combined with the information on brain weight loss, this suggests that personality changes in adults with Down syndrome may involve a sudden, abnormal process, and not normal aging. It will take much more research to test this possibility. However, the implication is that the onset of "active Alzheimer disease" in people with Down syndrome may have a specific cause. If true, some day it may be possible to discover that cause and perhaps even prevent it.

What does the future hold for treatment and prevention?

It has been suggested here that all adults with Down syndrome develop Alzheimer disease, but that it is expressed in persons with Down syndrome predominantly at the anatomical and biochemical levels; expression at the behavioral level occurs only occasionally. It is clear that careful medical attention is needed for older adults with Down syndrome to prevent any misdiagnosis of a treatable dementia, especially given the predisposition for hypothyroidism in the population wth Down syndrome (since this can produce an easily correctable dementia). For those adults with Down syndrome who do develop the severe dementia of the active form of Alzheimer disease, humane and appropriate care should be provided. Caregivers should be aware that at present there is little that can be done psychologically when active Alzheimer disease occurs among adults with Down syndrome (or anyone else) since substantial brain changes are involved. It is possible that some of the promising drug treatment approaches to Alzheimer disease may be of use for individuals with Down syndrome who develop active Alzheimer disease.

The possibility of prevention is remote at present. It requires much more information than we presently possess for both Alzheimer disease and Down syndrome. Concentrated effort is needed in a variety of disciplines, especially in the areas of brain biochemistry and epidemiology. Hope for effective treatment and prevention of dementia in the population with Down syndrome lie in the accumulation of research efforts. Given what is known now, these hopes can be justified.

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